REMARKS

The Drawings, which were Figure 9-9d, have been revised and are now Figures 9a-9e; Replacement Drawing Pages for those pages have been provided. The corresponding pages in the specification, which refer to Figures 9-9d, have been also revised.

The original Claims 1-39 have been canceled. Claims 40-51 are pending. These correspond in general to Claims 1,31; 7-16; and 26,29, respectively. Claims not being examined have been canceled; Applicants reserve the right to file divisional applications directed to this subject matter.

The application was rejected under 35 U.S.C. § 112, second paragraph; as well as 35 U.S.C. § 102(b), and 35 U.S.C. § 103(a). The claims were also rejected for being indefinite; lacking novelty and as being obvious.

THE REJECTION UNDER 35 U.S.C. § 112, second paragraph

The Office Action rejects claims 1-16 and 26-31 under 35 U.S.C. § 112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

Applicants respectfully submit that the new claims presented in this amendment are definite in that they particularly point out and distinctly claim that which Applicants regard as the invention.

The newly added Claim 40, is supported by the specification at page 7, lines 5-10 and Page 3, lines 30-31, also Claims 1 and 31. The association of the drug, metabolizing phenotype with the cytochrome CYP3A5 expression is supported by the specification at page 3, first paragraph and page 9, second full paragraph. Claim 41 provides that the amplification takes place during the screening process, as supported by the specification at pages 7 and 8.

The antecedent bases of various terms in Claims 42-51 are also clarified by usage in the independent claims 40, 42 as well as the dependent claims thereto.

The language of the newly added claims is believed to overcome all grounds of rejection. Reconsideration and withdrawal of the rejections is respectfully requested.

THE REJECTION UNDER 35 U.S.C. § 102(b)

The rewritten Claims now provide the language for identifying individuals or phenotypes as well as steps of disease diagnosis, and are not anticipated by the Jounaidi reference. Accordingly, the rejection should be considered and withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a)

The claims were rejected over the combination of Jounaidi and the Meyer EP specification. This rejection should be reconsidered and withdrawn, for the following reasons.

The key aspect of this resides not in the methodology used to identify different CYP3A5 gene variants, but in the fact that it has now been established that two polymorphisms, located in putative transcriptional regulatory regions, are linked and cause not only an increased CYP3A5 gene expression but also affect the metabolic activity of the thus obtained CYP3A5 isoform.

The Jounaidi et al., reference provides the 5'-flanking region of CYP3A5 with a comparison of two clones from different genomic libraries. From this comparison it appears that all mismatches are located upstream from the CATAA box (see figure 2 and page 1746 second paragraph), with some of them located in the consensus sequences for transcription factors namely the basic transcriptional element (BTE), the CAAT box (CAAT), the estradiol responsive element (ERE) and the activator protein-3 motif (AP-3). The present invention differs from the Jounaidi teaching in that it provides the role some of these mismatches play in the differential regulation of the CYP3A5 gene. In particular the concerted action of the variations at positions -475 (in particular T-475G) and -147 (in particular A-147G) on

CYP3A5 metabolic activity was not to be expected, was not disclosed or made obvious by Jounaidi or in combination with the Meyer reference.

As shown in the results section of the instant application, there is a strong linkage between the gene variations T-475G and A-147G; the present application proves that the group with the linked mutation has a higher metabolic ratio compared to the wild-type group. The unraveling of the genetic markers associated with the polymorphic metabolism of CYP3A5 has important consequences in the field of pharmacogenomics. The ability to predict metabolism by genotyping for the linked mutation, facilitates disease association studies and allows an explanation of adverse reactions or poor response to therapeutics which are metabolized by this cytochrome P450 isoform. In other words, with the characterization of the linked mutation and its implication on CYP3A5 metabolism it is now possible to diagnose subjects in having a low or high drug metabolizing phenotype associated with CYP3A5 expression. This linkage of mismatches and the implication thereof on the metabolic activity of CYP3A5 could not have been expected based on the combination of the cited prior art documents.

The present claims directed to a method of identifying high or low CYP3A5 drug metabolizing phenotypes based on the linked mutations T-475G and A-147G are unobvious over the references and are patentably distinct therefrom. Reconsideration and withdrawal of all the rejections, and allowance of the claims, is respectfully requested.

CONCLUSION

Favorable reconsideration of the application as amended is respectfully requested. The Examiner is respectfully requested to reconsider and withdraw the rejections. Applicants submit the Application is now in condition for allowance and respectfully requests early notice to that effect.

Should the Examiner feel that telephonic communication with Applicants' representative would further the prosecution of the instant application; she is invited to telephone the undersigned.

PETITION FOR EXTENSION OF TIME

Applicant(s) petition(s) the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated August 11, 2004 for two (2) months from November 11, 2004 to January 11, 2005.

Please charge Deposit Account No. 10-0750/JAB1462/LAD2 in the name of Johnson & Johnson for the cost of filing this Petition. Three copies of this page are included with this paper.

Respectfully submitted,

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JAB 1462 JAN 2005 amendment

Enclosures: Replacement Sheets 10/15, 11/15, 12/15, 13/15, 14/15, and 15/15

Date: January 11, 2005